Preliminary evaluation of the effects of blood flow on PET detection of ^{64}Cu-ATSM by dynamic gadolinium enhanced MRI in a rat tumour model.

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Background and Aims: Regional hypoxia within human tumours is a significant cause of treatment failure in many cancer sites. Non-invasive identification of hypoxic subvolumes would allow targeted radiotherapy dose escalation by intensity modulated radiotherapy to improve outcome; however a reliable non-invasive hypoxia marker is not yet available. ^{64}Cu-diacetyl-bis(N4-methylthiosemicarbazone) (^{64}CuATSM) is a radiolabelled tracer, detectable by PET scanning, currently being evaluated as a hypoxia marker. One report in a rodent model suggests that the uptake of the tracer in the first few minutes discriminates between hypoxia and normoxia. To assess the degree of influence of blood flow on marker uptake we have used gadolinium-enhanced dynamic MRI to monitor tumour blood flow in a rat tumour model immediately before injecting ^{64}CuATSM and monitoring marker uptake by dynamic PET scanning.

Methods: Eight BDIX rats with subcutaneous flank P22 carcinosarcoma were used. Anaesthetised rats were imaged using a portable, MRI and PET transparent jig in a 4.7 T horizontal bore magnet using a 6 cm rf coil. A sequence of 100 gradient echo images was obtained every 6 seconds (TR 60 ms, TE 2.5 ms, 1.0 mm slice thickness). After the first 30 seconds Gd-DTPA at 0.1 mMol.kg^{-1} was administered over 5 seconds via a cannulated tail vein at 6 ml.min^{-1} by means of an infusion pump. Immediately after completion of the MR acquisition, the rat was transferred without disturbance, in the same jig, to the PET scanner (MicroPET Focus 220, Concorde Microsystems Inc). ^{64}CuATSM (mean dose 25.6 MBq, range 10.0 – 60.3 MBq) was given as a bolus via the tail vein cannula at the start of a 60 minute dynamic attenuation-corrected PET scan.

Analysis: The AUC of the Gd-DTPA uptake curve over the first 90 seconds (AUC90) was calculated for the central axial slice of the tumour, processing the MR data with Varian software and Matlab. AUC90 has been shown to be a robust indicator of tumour blood flow in this tumour model. PET images were reconstructed and segmented in 10 minute time frames using Asipro software (Concorde Microsystems). A mean standardised uptake value was calculated for the central axial tumour slice (0.8 mm thick) over the first 10 minutes (SUV_{0-10}) and also for 50 – 60 minutes after injection (SUV_{50-60}). Correlation coefficients were then calculated for AUC90 and SUV_{0-10} and for AUC90 and SUV_{50-60}.

Results: Gd-DTPA images showed that blood flow tended to exhibit annular distribution at the periphery of the tumour, and early ^{64}CuATSM PET images also showed annular distribution of the marker. Distribution of ^{64}CuATSM to the central part of the tumour was frequently seen at the later time point, as in the example using transaxial slices shown below. The rat is on its right side with the tumour (indicated by arrows) uppermost. Maximum tumour diameter was ~ 15 mm.

Fig 1:
T1-weighted MRI before and 60 seconds after the start of Gd-DTPA infusion

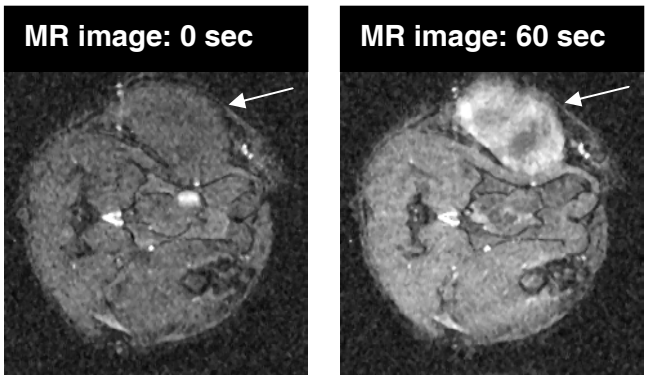
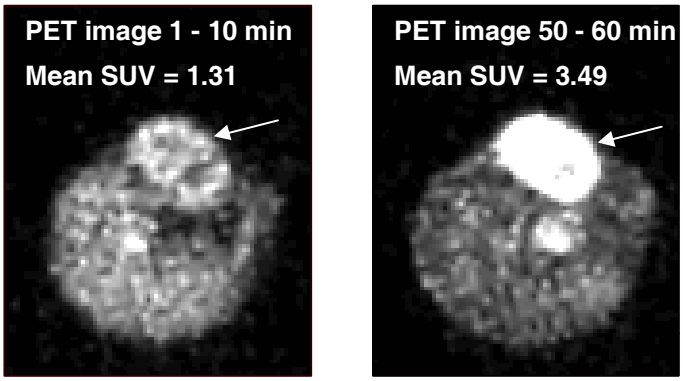


Fig 2:
Mean uptake of ^{64}CuATSM from 0 – 10 min and 50 – 60 min post injection.



The correlation coefficient R for AUC90 and SUV_{0-10} was 0.75 ($p = 0.043$), indicating a significant correlation between blood flow and early ^{64}CuATSM uptake. However the correlation coefficient for AUC90 and SUV_{50-60} was 0.44 ($p = 0.27$), showing that the uptake of ^{64}CuATSM by 50 – 60 minutes after administration was not directly correlated with blood flow to the tumour.

Conclusions: The statistically significant correlation observed between the blood flow parameter AUC90 for Gd-DTPA and ^{64}CuATSM uptake in the first 10 minutes suggests that in this model the early phase of marker uptake is dominated by blood flow. However, the apparent independence of blood flow of ^{64}CuATSM uptake by 50 – 60 minutes after administration points to a redistribution of marker within the tumour according to other factors, such as hypoxia. Work correlating ^{64}CuATSM uptake with immunohistochemical detection of a nitroimidazole hypoxia marker (pimonidazole) is in progress. The data suggest that clinical ^{64}CuATSM PET imaging should not be carried out immediately after tracer administration, as some time is required for dissipation of the early dominance of blood flow in determining the tracer uptake.